Revised Proposed Process for Preparation of the Report on Carcinogens ~~Review Process~~

December 7, 2011

The Report on Carcinogens (RoC) is a Congressionally mandated, biennial document that identifies and discusses agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") that may pose a hazard to human health by virtue of their carcinogenicity. Substances are listed in the report as either *known* or *reasonably anticipated human carcinogens*, and a description of the substance, its uses, potential sources of exposure, the rationale for listing, and applicable federal regulations are included in the RoC in a "substance profile." Each edition of the report is cumulative. The National Toxicology Program (NTP) prepares the RoC on behalf of the Secretary of Health and Human Services (HHS). Review of candidate substances and preparation of the ~~draft RoC~~report are managed by the Office of the Report on Carcinogens (ORoC) within the Division of the NTP, National Institute of Environmental Health Sciences (NIEHS).

A schematic of the process for preparation of the RoC is provided in Figure 1. The process has four parts: (1) nomination and selection of candidate substances, (2) scientific evaluation of candidate substances, (3) public release of the draft RoC monograph and peer review, and (4) HHS approval and release of the latest edition of RoC. Each part is described below.

Nomination and Selection of Candidate Substances

The NTP invites nominations of substances for consideration for listing in the RoC from anyone in the public and private sectors. A nomination may seek to list a new substance in the RoC, reclassify the listing status for a substance already listed, or remove a substance already listed. Nominations may be submitted by mail or fax to ORoC[1] or on-line at *http://ntp.niehs.nih.gov/go/27911*.

A nomination should contain a rationale or reason for the RoC review and, if possible, appropriate background information and relevant data to support the rationale (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer Monographs, exposure surveys, release inventories).

ORoC initially evaluates the nomination to determine whether there is sufficient information on exposure and carcinogenicity to justify its formal evaluation and consideration for the RoC. ORoC shares nominations with its agency partners.[2] The NTP solicits public comments on the

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[2] Interagency review is invited from agencies represented on the NTP Executive Committee, including the Consumer Product Safety Commission, Department of Defense, Environmental Protection Agency, Food and Drug Administration, National Cancer Institute, National Center for Environmental Health/Agency for Toxic Substances

nominations in the *Federal Register*, including a request for information about ongoing studies, recent publications, current production, use patterns, sources of exposure, and the names of scientific experts with relevant knowledge, as well as scientific issues important for assessing the carcinogenicity of the substance. Public comments received on the nominations are posted on the RoC website (*http://ntp.niehs.nih.gov/go/roc*). The NTP considers the interagency and public comments and identifies nominations for evaluation for the RoC. Those nominations proposed for evaluation proceed as discussed below. The NTP notifies the nominators for those nominations not selected.

ORoC prepares a draft concept document for each substance proposed for evaluation. The concept for a substance is a brief document that ~~(1)~~ outlines the rationale for the nomination of the substance~~'s~~ for review for the RoC including information on exposure, extent and nature of the scientific evidence for evaluating carcinogenicity in humans and experimental animals, and any ~~currently identified~~ major relevant issues such as any proposed mechanisms or modes of action of carcinogenicity. ~~and~~ The concept document also ~~(2)~~ lays out the proposed approach for development of the cancer evaluation component of the draft RoC Monograph on the substance including the search strategy for identifying relevant scientific literature and for obtaining external scientific and/or public inputs [see Scientific Evaluation of Candidate Substances]. The NTP announces one or more proposed substances for evaluation and solicits public comments on draft concepts through announcements in the *Federal Register* and NTP publications.

The NTP presents the draft concept for a substance to the NTP Board of Scientific Counselors (BSC)[3] at a public meeting with opportunity for public comment.[4] The BSC is asked to comment on the draft concept for a proposed substance, including (1) the rationale for its review for the RoC and (2) the proposed approach for obtaining external scientific and public inputs in development of the cancer evaluation component of its draft RoC Monograph. The NTP considers the BSC comments and public comments, and the NTP Director makes the final determination whether to add the substance to the list of candidate substances for RoC evaluation. Concepts for approved candidate substances are finalized based upon BSC comments and public comments and posted on the NTP RoC website (*http://ntp.niehs.nih.gov/go/roc*). The NTP maintains the complete list of candidate substances on the NTP RoC website. The list includes all substances for which concepts have been approved for review, but ~~listing~~ placement on this list does not necessarily imply that the substance will undergo review for any specific edition of the RoC.[5]

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and Disease Registry, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health, and Occupational Safety and Health Administration.

[3] The BSC is a federally chartered advisory committee whose members are appointed by the Secretary of HHS. The BSC provides advice to the NTP Director on matters relating to scientific program content and evaluates the scientific merit of the NTP's intramural and collaborative programs; *http://ntp.niehs.nih.gov/go/164.*

[4] NTP practice is to allot seven minutes per speaker, one speaker per organization, for presentation of oral public comments.

[5] The NTP may defer or terminate the review of a candidate substance for the RoC at any time if relevant information becomes available that warrants its reconsideration or if scheduling issues preclude completion of a timely review. In such cases, the nominator, the BSC, the NTP Executive Committee, and the public are notified of this action.

Scientific Evaluation of Candidate Substances

ORoC prepares a draft RoC Monograph for ~~a~~ each candidate substance. The ~~draft~~ RoC Monograph has two parts: (1) a cancer evaluation component that reviews all information that may bear on a listing decision, assesses its quality and sufficiency for reaching a listing decision, ~~and~~ applies the RoC listing criteria[6] to the relevant scientific information, and recommends a listing status for the candidate substance in the report and (2) a substance profile that contains the NTP's preliminary listing recommendation and a summary of the scientific evidence ~~for carcinogenicity supporting~~ considered key to reaching that recommendation.

In general, the cancer evaluation component addresses the following topics, although other topics may be included when relevant to evaluating the carcinogenicity of the candidate substance:

- properties (e.g., chemical, physical, or biological), production, and use
- human exposure
- toxicokinetics[7]
- cancer studies in humans
- cancer studies in experimental animals
- ~~toxicokinetics and~~ mechanisms of ~~carcinogenicity~~cancer induction and other related effects

Information on exposure and properties of the candidate substance must be publicly available. All scientific information used to evaluate the potential carcinogenicity of a candidate substance must come from publicly available, peer-reviewed sources.

The cancer evaluation component for a candidate substance: (1) presents the search strategy and the inclusion/exclusion criteria for the resultant literature, (2) identifies and describes the relevant studies for the RoC evaluation, (3) provides an assessment of the quality of individual studies and discusses their use for informing the evaluation of carcinogenicity, (4) provides an assessment of the level of evidence for human studies or experimental animal studies in applying the RoC listing criteria, and (5) integrates the overall body of evidence (human, animal, mechanistic) and reaches a preliminary listing recommendation for the substance in the RoC.

The nature, extent, and complexity of the scientific information on a candidate substance guides the approach used by the NTP to develop the cancer evaluation component. The approach is tailored to enable ORoC to ~~use the most appropriate mechanism(s) to~~ obtain external advice and address scientific issues for assessing the carcinogenicity of a given candidate substance and may vary among substances. The approach may include external scientific input (e.g., expert panel,[8]

[6] RoC listing criteria are the standards against which the scientific evidence for carcinogenicity is evaluated to determine whether to list a candidate substance in the RoC, and if so, as a *known human carcinogen* or *reasonably anticipated human carcinogen*. The criteria are available at *http://ntp.niehs.nih.gov/go/15209*.

[7] Toxicokinetics describes the rate that a chemical enters the body and how it is handled within the body. Renwick AG. Toxicokinetics: Pharmacokinetics in Toxicology. In *Principles and Methods of Toxicology, Fourth Edition.* Hayes AW. ed. London: Taylor & Francis, pp. 137-192.

[8] NTP panels are federally chartered, technical, scientific advisory groups convened on an as needed basis to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge selected by the NTP from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with the Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166.*

workshop, individual technical advisors), public input (e.g., listening session, comment), and/or interagency input. All public comments received during the evaluation become part of the public record, are posted on the RoC website, and are considered by the NTP and/or any external advisors during subsequent steps in the process.

ORoC completes the draft cancer evaluation component with consideration of all inputs to its development. Based on the draft cancer evaluation component, ORoC prepares the draft substance profile. These two documents are compiled to form the draft RoC Monograph.

The NTP requests comment on the draft RoC Monograph from its partner agencies, considers this input, and completes the draft monograph. ~~The NTP considers this input and, as appropriate, revises the prepares a revised draft RoC Monograph for public comment and peer review.~~

Public Release of Draft RoC Monograph and Peer Review

The NTP releases the ~~revised~~ draft RoC Monograph for public comment and then convenes a meeting of an external ~~advisory~~ scientific ~~group~~ panel[9] ~~(e.g., BSC or expert panel)~~ to peer review the ~~revised~~ draft RoC Monograph. The NTP publishes a *Federal Register* notice prior to the meeting announcing the peer review and availability of the ~~revised~~ draft RoC Monograph and inviting written public comment. The public is also invited to attend the meeting and provide oral comments.

The NTP sets aside time at the meeting for discussion of scientific issues raised in the public comments. The peer-review charge is twofold: (1) to comment on the cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria, and (2) to comment on the substance profile, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the listing status of the candidate substance in the RoC. The panel votes on (1) whether the scientific evidence supports the NTP's level of evidence for human studies or experimental animal studies and (2) whether the scientific evidence supports the NTP's preliminary listing decision. A ~~peer-review~~ report of the deliberations by the ~~expert~~ peer-review panel ~~or BSC~~ is prepared and posted on the RoC website.

ORoC considers the peer-review report, prepares the NTP's response to the peer-review report, and posts the response on the RoC website. Based upon the peer-review comments, ORoC prepares a revised draft RoC Monograph. The NTP provides the BSC information regarding the peer review at a public meeting. Following the meeting, ORoC in concert with the NTP Director, ~~and~~ finalizes the RoC Monograph on the candidate substance, including the cancer evaluation component and substance profile, ~~. The NTP~~and posts the ~~revised draft~~final ~~RoC M~~monograph on the RoC website. ~~The NTP prepares a response to the peer review report that is released to the public when the next edition of the RoC is released (see below).~~

[9] See footnote 8.

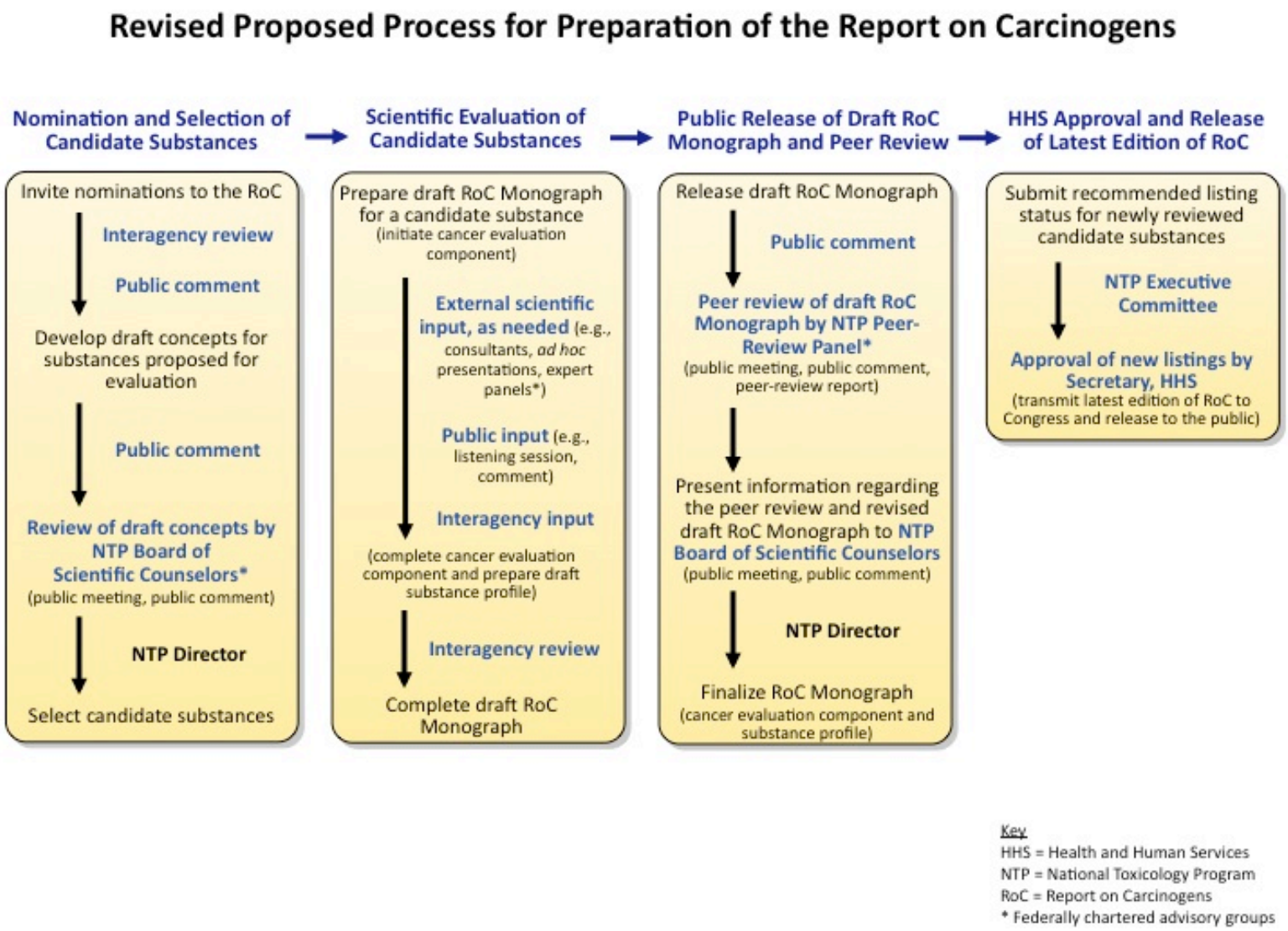
HHS Approval and Release of Latest Edition of RoC

~~Every two years, t~~The NTP submits newly reviewed candidate substances with recommended listing status to the NTP Executive Committee[10] for consultation and then to the Secretary of HHS for review and approval. The substance profiles for new listings approved by the Secretary are added to the RoC, and the next edition of the report in electronic format is prepared, transmitted to the Congress, and published on the RoC website for the public. Periodically, the NTP will publish the RoC in both printed and electronic formats, depending upon demand for the printed version.

The NTP publishes a notice in the *Federal Register* and NTP publications announcing the listing outcome for each candidate substance that underwent formal review for the RoC and the availability of the next edition of the RoC. ~~At that time, the NTP posts its response to the peer-review report on the RoC website.~~

[10] The NTP Executive Committee is composed of the heads (or their designees) of nine federal participating agencies, listed in footnote 2, and provides advice to the NTP on policy issues; *http://ntp.niehs.nih.gov/go/163*.

Figure 1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Nomination and Selection of Candidate Substances
Scientific Evaluation of Candidate Substances
Public Release of Draft RoC Monograph and Peer Review
HHS Approval and Release of Latest Edition of RoC
Invite nominations to the RoC
Interagency review
Public comment
Develop draft concepts for substances proposed for evaluation
Public comment
Review of draft concepts by NTP Board of Scientific Counselors*
(public meeting, public comment)
NTP Director
Select candidate substances
Prepare draft RoC Monograph for a candidate substance
(initiate cancer evaluation component)
External scientific input, as needed (e.g., consultants, ad hoc presentations, expert panels*)
Public input (e.g., listening session, comment)
Interagency input
(complete cancer evaluation component and prepare draft substance profile)
Interagency review
Complete draft RoC Monograph
Release draft RoC Monograph
Public comment
Peer review of draft RoC Monograph by NTP Peer-Review Panel*
(public meeting, public comment, peer-review report)
Present information regarding the peer review and revised draft RoC Monograph to NTP Board of Scientific Counselors
(public meeting, public comment)
NTP Director
Finalize RoC Monograph
(cancer evaluation component and substance profile)
Submit recommended listing status for newly reviewed candidate substances
NTP Executive Committee
Approval of new listings by Secretary, HHS
(transmit latest edition of RoC to Congress and release to the public)
Key
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups